REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 2, 8, 68 and 69 are currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 2-4, 8, 11-12, 14, 16-21, 23-29, 32-41, 43-51 and 62-75 are now pending in this application.

A. Claim Amendments

The Examiner requested that references to "TNFα protein" in the claims be changed to "TNFα." The requested change has been made where the phrase "TNFα protein" appeared; i.e., in Claims 2, 8, 68 and 69. Entry of the proposed amendments is therefore requested.

B. Specification Amendments

The Examiner requested that the Title and Abstract each be amended to refer to the embodiment of the invention that is claimed. The requested changes have been made. Entry of the proposed amendments is therefore requested.

C. Response to Obviousness Rejection Based on Kipps, et al. and Mueller, et al.

The Office Action sets forth a rejection of *Claims 14, 16-21, 23-26, 43-51 and 62-67* for obviousness under 35 U.S.C. § 103 in view of US Patent No. 7,070,771 to Kipps, et al. and/or corresponding PCT Published Application, WO 98/26061 (collectively, the "Kipps Application") in combination with the disclosure of a 1999 paper by Mueller, et al. (*J.Biol.Chem.* 274:38112-

38118; "Mueller"). However, *Claims 14, 16-21, 23-26, 43-51 and 62-67* were previously withdrawn as not pertaining to the elected invention. Therefore, for purposes of compact prosecution, Applicant will respond to the rejection as having been made with respect to the pending claims, which are Claims 2-4, 8, 11-12, 14, 16-21, 23-29, 32-41, 43-51 and 62-75.

The Kipps Application is relied upon for its teachings regarding chimeric TNF family ligand molecules composed of domains of different TNF family molecules, including the CD154 chimeric molecules. The Office Action concedes that the particular nucleic acid molecules claimed are not taught in the Kipps Application (Action at page 4).

The Mueller paper is relied upon for its suggestion that elimination of secreted TNFα from circulation has a desirable impact on the immune system, and that such elimination can be achieved by preventing cleavage at proteolytic cleavage sites in the TNFα molecule. Together, the Examiner contends that the Kipps Application and Mueller teach chimeric CD154/ TNFα molecules which lack proteolytic cleavage sites and do not produce soluble TNFα.

Applicant respectfully disagrees. Mueller only teaches the biological effects of modifying wild-type TNFα in one of three respects: deleting 3 amino acids at the +1 cleavage site murine (mutant L1); deleting three amino acids at the -10 cleavage site (mutant L2); deleting the same three amino acid loci at both +1 and -10 (mutant L3); and additionally inactivating (but not deleting) a third residue at position +11 (mutant L6) (Mueller, at page 38114). Contrary to the present invention none of the Mueller mutants tested consist of molecules in which any portion of Domain III of the molecule is modified (e.g., per Claim 2) or in which all of the Domain IV cleavage site is deleted (per Claim 8). Nor are any of the Mueller mutants human in origin (although the Kreigler, *et al.* reference cited at page 38112 of Mueller describes a human TNF molecule from which a cleavage site in Domain IV has been removed).

Furthermore, while soluble TNF release can be reduced in *certain* cell types by blocking cleavage sites, the technique is not effective in all cell types. For example, in Mueller, soluble TNFα release was prevented by the murine L6 mutant in NIH-3T3 cells, but was released from

By155.16 cells transfected with any of Mueller's mutants (Mueller, at page 38116-38117, bridging paragraph). Figure 5 of the present Specification confirms that soluble TNFα release is not affected in all cell types by mutation of cleavage sites in the molecule.

In the Figure, data for the 'Ad-^{2}TNF' molecule (from which the TACE cleavage-site was entirely removed) still produced copious quantities of soluble TNFα in HT1080 cells (human lung carcinoma). These results were confirmed by the inventors in a variety of other cell types, in which soluble TNF release from the Ad-^{2}TNF molecule was 1000 to 50,000 times higher than from a molecule according to Claim 2 (see, Declaration of Charles Prussak submitted herewith, at ¶¶ 8 and 9, including Table 1; the molecule of the invention is referred to as CD154-TNF and lacks the TACE cleavage site in both CD154 Domain III and TNFα Domain IV [see, Declaration at ¶ 5]). Therefore, the effect of altering cleavage sites in the TNFα molecule on soluble TNFα release in various cell types is not predictable. As such, the Mueller disclosure is at best an invitation to experiment in hope of identifying additional cell types, if any, in which his success in NIH-3T3 cells might be obtained.

In contrast, the present invention substantially eliminates release of soluble TNF in a variety of cell types by using a chimeric TNFα ligand polypeptide that has the proximal extracellular domain (III) from CD154 [domain III] from which a metalloproteinase cleavage site has been removed and joined (directly or indirectly) to a fragment of the extracellular domain (IV) of TNF (Claim 2).For example, using a CD154/TNFα chimera lacking the TACE cleavage-site from both Domain III of the CD154 element (consisting of its Domains I-III) and from the TNFα Domain IV (CD154:TNF, as defined at Table II of the Specification, page 22) resulted in virtual elimination of soluble TNF release from the chimeric molecules is achievable in a variety of cell types (see, Figures 4 and 5, data for CD154:TNF in HT1080 and CLL cells; and the Declaration of Charles Prussak submitted herewith, at ¶ 9, Table 1—data from HT1080, A549, HeLa, RPMI-8226 and HT1376 cells; and Specification at page 32, ¶ [0111]: similar results obtained in COLO205, 293, HCT15, PC3, RPMI18226 and BT20 cells).

These data demonstrate that the CD154/TNF molecules claimed have a unique and unexpectedly robust ability to eliminate soluble TNFα release in a variety of cell types. Nothing in the prior art would lead one to realize that joining Domain IV of TNFα to Domain III of CD154 (one of a number of chimeric structures suggested by the Kipps Application) and blocking metalloproteinase cleavage in Domain III (optionally also in Domain IV) would have the comprehensive impact on soluble TNFα achievable with the molecules claimed. Simply replacing Domain III of the TNFα molecule with Domain III of another TNFα molecule (e.g., CD70) per the Kipps Application is not sufficient to this end (see, Prussak Declaration at ¶¶ 12-14), nor is replacing the TNF Domain III with the CD154 Domain III entirely satisfactory (see, ¶ [0116]).

Applicants therefore respectfully submit that the invention claimed has a structure not taught in the prior art, and provides unexpected properties. As such, the invention represents a non-obvious advance over the teachings of the Kipps Application and Mueller (see, e.g., *Knoll Pharmaceutical Company, Inc. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381 (Fed.Cir., 2004), evidence of unexpected results obtainable from a claimed combination of hydrocodone and ibuprofen sufficient to prove non-obviousness; note also *Knoll's* holding that such evidence may be produced after the filing date).

Reconsideration and withdrawal of the rejection under § 103 is respectfully requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Atty. Dkt. No. 041673-2092

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 10-5-06

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